LYMErix
Lyme Disease Vaccine (Recombinant OspA)

Safety Assessment for Licensure

Francois P. Meurice, M.D.

Director Clinical Development
GSK Biologicals

Introduction

- Clinical data available for licensure
- Safety information from the large pivotal Lyme 008 trial
- Areas of special interest
  - Influence of vaccination on LD manifestations
  - Previous LD History
  - (Autoimmune) Arthritis
  - HLA type and Musculoskeletal Symptoms
  - Neurologic/Cardiac events

Phase I

Study	Enrollment (per group)	Objectives	Schedule (months)	Duration (months)
001	24 (12/12)	Safety/Immuno	0, 1, 2	6
002	60 (20/20/20)	Safety/Immuno	0, 1, 2	24
003	240 (80/80/80)	Safety/Immuno	0, 1, 2	3
004	90 (30/30/30)	Safety/Dose Selection	0, 1, 2	3

Phase II

Study	Enrollment (per group)	Objectives	Schedule (months)	Duration
005	353 (89/87/88/89)	Dose Range/Safety HLA Typing	0, 1, 2	12 months
007	30 (5/5/20)	Safety and Previous LD	0, 1, 2	6 months
009	90 (30/60)	Safety/Immuno	0, 1, 2	13 months
010	40 (20/20)	Immuno	0, 1	2 months
015	250 (125/125)	Dose Selection/Safety Pediatric Population	0, 1, 2	3 months

Phase III

Study	Enrollment (per group)	Objectives	Schedule (months)	Duration
008	10,936 (5469/5467)	Pivotal Efficacy Safety Immuno	0, 1, 12	20 months
013	9,991 observed 4,300 vaccinated	Safety Placebo Crossover	4 months safety placebo crossover 0,1, 12	17 months
014	800 (400/400)	Immuno Lot Consistency Alternate Schedule	0, 1, 6 or 0, 1, 12	13 months
016	~ 1,000 (500/500)	Safety Immuno	0, 1, 2, 12 or 0, 1 , 12	13 months
017	~ 350 (175/175)	Safety/Booster	Booster	36 months
018	~ 35	Immuno	0, 7, 28 days	2 months
019	240 (60/60/60/60)	Lot Consistency/ Immuno	0, 1	3 months

Overview - Prelicensure Clinical Data

- At time of BLA, a total of 16 studies were either completed or ongoing
- A total of 6,478 subjects received the final LYMErix formulation (18,047 doses)

Pivotal Safety and Efficacy Study - Lyme 008

- **Study Design / Objective**

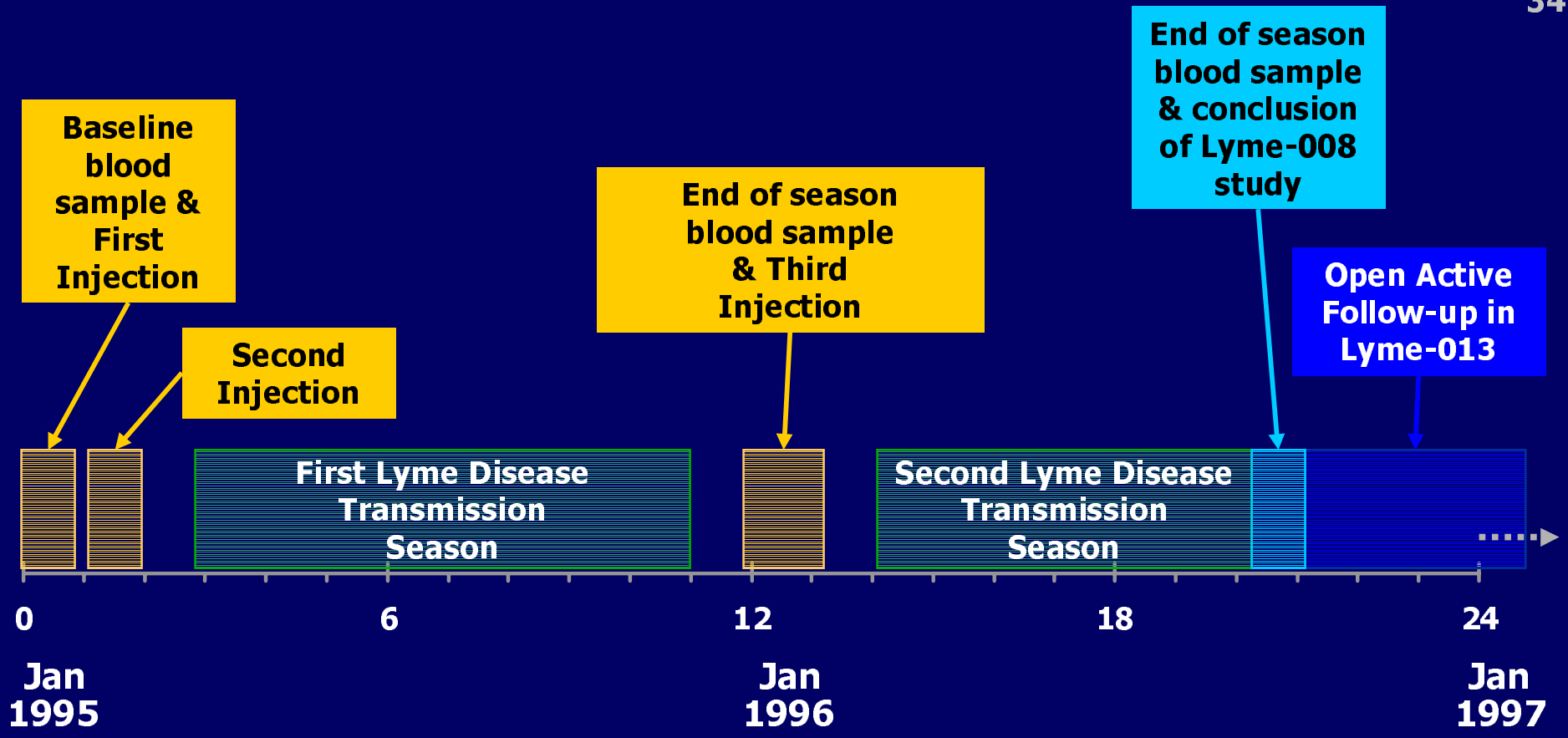
  Double blind, placebo control, multicenter, randomized study to evaluate safety, immunogenicity, and protective efficacy of a recombinant Lipo-OspA (LYMErix) vaccine in healthy adults

- **Inclusion criteria:**

  Healthy individuals between 15 and 70 years of age from Lyme endemic areas

- **Exclusion criteria:**

  Chronic joint or neurologic illness related to LD, current disease with joint swelling or musculoskeletal pain, current LD, 2nd/3rd AV block, pacemaker, immunosuppression, and pregnancy



Timeline for Vaccine Study

Pivotal Safety and Reactogenicity Data

- **24 months safety data follow-up in the Lyme-008/-013 cohort**
- **AEs collected as:**
  - **Unsolicited**
    - Early onset (≤ 30 days)
    - Late onset (>30 days)
  - **Solicited**
    - Diary card subset
  - **Symptoms suspect for LD**

Unsolicited AEs Occurring Within 30 Days (Overall)

- **Statistically significant differences between the vaccine and placebo groups**
  - **Local symptoms**
    - injection site pain (21.9% vs. 6.9%)
    - injection site reactions (1.5% vs. 0.9%)
  - **General symptoms**
    - fever (2.6% vs. 1.6%)
    - influenza-like symptoms (2.5% vs. 1.7%)
    - myalgia (4.8% vs. 2.9%)
    - chills/rigors (2.1 vs. 0.7%)

Unsolicited AEs with Onset More Than 30 Days After Vaccination (Overall)

- No statistically significant differences were found between placebo recipients and vaccinees
- No increase in AEs with successive doses

Local and General Solicited AEs Reported (Overall)

	Overall	
	V (N = 402) %	P (N = 398) %
Local Symptoms		
Redness, any	41.8	20.9
Severe	4.2	0.0
Soreness, any	93.5	68.1
Severe	5.0	0.5
Swelling, any	29.9	11.3
Severe	0.5	0.0
General Symptoms		
Arthralgia, any	25.6	16.3
Severe	1.0	0.5
Fatigue, any	40.8	32.9
Severe	3.0	2.3
Headache, any	38.6	37.2
Severe	3.0	2.8
Rash, any	11.7	5.3
Severe	0.2	0.0
Fever $\geq$99.5°F	3.5	2.3
>102.2°F	0.0	0.0

- Statistically significant differences between vaccine and placebo groups for:
  - Local symptoms at injection site
  - Several flu-like symptoms (including fatigue and arthralgia), and rash
- No difference for headache or fever
- Mean durations of general solicited symptoms: 1-8 days (range 1-236)

Serious Adverse Events (SAEs)

- **SAE definition:**
  - **Any event which is fatal, life threatening, disabling or incapacitating, results in or prolongs hospitalization, or any experience which the investigator regards as serious**

- **In addition, pregnancies, and arthritis/arthralgia lasting for more than 30 days, were reported in a similar manner (within 24 hours)**

Serious Adverse Events (SAEs)

- 581 vaccine and 586 placebo recipients reported SAEs
- No statistical difference by body system
- 14 vaccine and 15 placebo recipients experienced SAEs designated as related or possibly related
- No deaths attributable to the vaccine

Safety Conclusions

- Unsolicited AEs with onset ≤ 30 d
  - more in vaccine than placebo recipients
- Unsolicited AEs with onset > 30 d
  - no difference between vaccine and placebo recipients
- Solicited AEs
  - 97% vaccine and 82% placebo (at least 1 symptom)
  - soreness - most common local symptom
  - headache and fatigue - most common systemic symptoms
  - ≤ 5% of solicited symptoms were rated "severe"
- SAEs
  - no difference between vaccine and placebo

Areas of Special Interest

- Influence of vaccination on LD manifestations
- Subjects with previous LD
- Induction of autoimmune arthritis
- HLA type and musculoskeletal symptoms
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Influence of Vaccination on LD Manifestations

- No interference with the ability to confirm LD diagnosis by culture, PCR, or WB
- No masking, attenuation, or alteration of the clinical presentation of LD
- No increase in the rate of asymptomatic infection
- No effect on the duration of EM
- No influence on treatment of breakthrough cases

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Subjects with Previous Lyme Disease

- **Do subjects with previous LD have more symptoms?**
- **2 ways of assessing LD history**
  - **Self-reporting**
  - **WB positivity**
    - Baseline WB done when WB(+) at 12 or 20 months, or suspected LD with positive or equivocal WB

AEs in Subjects Self-Reporting Previous LD

		History vs. No History Vaccinees	History vs. No History Placebo
Musculoskeletal	(early)	↗	=
	(late)	↗	↗
Psychiatric	(early)	↗	↗
	(late)	↗	↗
Nervous System	(late)	↗	↗
GI disorders	(late)	↗	↗

AEs in Subjects Self-Reporting Previous LD

		Vaccinees			Placebo		
		History + (N=610) %	History - (N=4,859) %	p value	History + (N=596) %	History - (N=4,871) %	p value
Musculoskeletal	(early)	20.00	13.38	≤ .001	12.8	11.1	.243
	(late)	33.11	21.75	≤ .001	34.9	20.9	≤ .001
Psychiatric	(early)	2.30	1.19	.024	2.85	0.94	≤ .001
	(late)	4.26	2.74	.035	5.20	2.73	≤ .001
Nervous System	(late)	22.62	12.64	≤ .001	21.81	12.87	≤ .001
GI disorders	(late)	6.89	4.82	.028	8.05	5.67	.020

AEs in Subjects in WB (+) Subjects

		WB(+) vs. WB(-) Vaccinees	WB(+) vs. WB(-) Placebo
Musculoskeletal	(early)	=	=
	(late)	=	=
Psychiatric	(early)	=	=
	(late)	=	=
Nervous System	(late)	=	=
GI disorders	(late)	=	=

AEs in WB(+) Versus (-)

		Vaccine			Placebo		
		WB(+) N=124	WB(-) N=5,345	P Value	WB(+) N=126	WB(-) N=5,341	P Value
Musculoskeletal	(early)	13.7	14.1	.895	9.5	11.4	.519
	(late)	25.8	23.0	.456	28.6	22.3	.095
Psychiatric	(early)	1.61	1.31	.679	2.38	1.12	.177
	(late)	3.23	2.90	.784	3.97	2.98	.430
Nervous System	(late)	12.10	13.98	.550	14.29	13.84	.885
GI Disorders	(late)	1.61	5.13	.077	3.17	5.99	.186

Previous Lyme Disease Conclusions

- Self-Reported LD
  - Increased incidence of AEs in BOTH vaccinees and placebo recipients
  - Exception to above was seen for early musculoskeletal AEs (increased incidence was not seen in placebo recipients)
- Western Blot
  - Nature and incidence of AEs (early or late) did not differ between WB(+) subjects as compared to WB(-) subjects

WB confirmed previous LD has no impact on safety profile

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Induction of Autoimmune Arthritis?

- No increased incidence of arthritis in vaccinees:

	Vaccinees	Placebos
	n (%)	n (%)
onset ≤ 30 days	50 (0.9)	44 (0.8)
onset > 30 days	159 (2.9)	155 (2.8)

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Treatment-resistant Lyme arthritis

The hypothesis - ***Gross et al. (1998) Science 31, 281***

- **TRLA is an autoimmune disease triggered by natural infection**
- **This autoimmune disease may be the result of a cross-reactivity between OspA and hLFA-1**
- **HLA-DR4 individuals are at risk of developing TRLA after natural infection**

HLA typing in Lyme - 005

- 338/353 tested for HLA DR 4 and 2 Types:
  - DR 4 (+): 32% of subjects
  - DR 2 (+): 0.8%
- Results: 4 cases of unspecified arthritis
  - 1 DR 4 (+) in placebo group
  - 1 DR 4 (+) in vaccine group

HLA Typing in 2 subsets of Lyme - 008

- **1st subset**
  - **85 consecutive samples at one site (41 vaccinees, 44 placebo recipients)**
  - **Similar HLA profile in vaccinees with vs without pain or inflammation at injection site**
- **2nd subset**
  - **For 9/12 subjects from the entire study population with *unexplained* arthritis or tendinitis, HLA typing was available**
    - 1/4 in the vaccine group HLA DR4 (+)
    - 1/5 in the placebo group HLA DR4 (+)

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Neurologic and Cardiac events

- No difference in neurologic or cardiac events in vaccinees and placebo recipients
- All AEs of interest were reviewed by an independent panel of experts

Conclusion

- Large body of safety data accrued prior to licensure
- Acceptable safety profile in clinical trials albeit moderate reactogenicity
- No clinical evidence (including from HLA typing) supporting theoretical concerns
- Demonstrated efficacy in definite (78%) and asymptomatic (100%) LD

LYMErix considered safe and effective and approved for prevention of Lyme disease